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APPLICATION NUMBER:

21-226/S-002

21-251/S-002

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Memorandum of Project Manager's Review: Supplemental Labeling Review with Draft Labeling

NDA: 21-226/S-002
21-251/S-002

Date submitted: January 2, 2001
Date received: January 3, 2001
Date completed: March 8, 2001

Sponsor: Abbott Laboratories
D-491/AP6B-1SW
100 Abbott Park Road
Abbott Park, IL 60064-6108

Product: Kaletra™ (lopinavir/ritonavir) Capsules
Kaletra™ (lopinavir/ritonavir) Oral Solution

Materials Reviewed:

1. Draft label submitted with Labeling Supplement dated January 2, 2001.
2. Draft label submitted with Amended Labeling Supplement dated January 30, 2001.

Background
The January 2, 2001 Labeling Supplement (S-002) was submitted by the Sponsor revising the pediatric dosing tables in the Package Insert (PI).

Revisions

The following revisions were made to the **Pediatric Patients** subsection under the **DOSAGE AND ADMINISTRATION** section of the PI (additions are underlined and deletions have ~~strike thru~~):

DOSAGE AND ADMINISTRATION

Adults
The recommended dosage of KALETRA is 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **CLINICAL**

PHARMACOLOGY – Drug Interactions and/or **PRECAUTIONS** – Table 6).

Pediatric Patients

In children 6 months to 12 years of age, the recommended dosage of KALETRA oral solution is 12/3 mg/kg for those 7 to <15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice daily taken with food, up to a maximum dose of 400/100 mg in children >40 kg (5.0 mL or 3 capsules) twice daily. [redacted] It is preferred that the prescriber calculate the appropriate milligram dose for each individual child ≤ 12 years old and determine the corresponding volume of solution or number of capsules. However, as an alternative, the following table contains dosing guidelines for KALETRA oral solution based on body weight. When possible, dose should be administered using a calibrated dosing syringe.

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
Without nevirapine or efavirenz		
7 to <15kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
>10 to <15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
>20 to 25 kg		[redacted] 2.75mL
>25 to 30 kg		[redacted] 3.5mL
>30 to 35 kg		4.0mL
[redacted]		[redacted]
>35 to 40 kg		4.75mL
>40 kg	Adult dose	5mL (or 3 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

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Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA oral solution to 13/3.25 mg/kg for those 7 to <15 kg and 11/2.75 mg/kg for those 15 to [redacted]5 kg (approximately

equivalent to 300/75 mg/m^2) twice daily taken with food, up to a maximum dose of 533/133 mg in children ≥45 kg twice daily should be considered when used in combination with efavirenz or nevirapine in treatment experienced children 6 months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz or nevirapine in children (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
With nevirapine or efavirenz		
7 to <15 kg	13 mg/kg BID	
7 to 10 kg		1.5 mL
>10 to <15 kg		2.0 mL
15 to 45 kg	11 mg/kg BID	
15 to 20 kg		2.5 mL
>20 to 25 kg		3.25 mL
>25 to 30 kg		4.0 mL
>30 to 35 kg		4.5 mL
>35 to 40 kg		5.0 mL (or 3 capsules)
>40 to 45 kg		5.75 mL
> 45 kg	Adult dose	6.5 mL (or 4 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

Conclusions/Recommendations

The above changes to the KALETRA® label are acceptable. Draft labeling is attached. Please see the Medical Officer's memorandum for concurrence. An approval letter based on draft labeling will be issued to the Sponsor.

Sean J. Belouin, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

Concurrence:

HFD-530/CRPM/DeCicco-TD-3/9/2001
HFD-530/MOTL/Murray-JSM-3/8/2001
HFD-530/MO/Lewis-LLL-3/8/2001
HFD-530/RRO/Struble-KAS-3/8/2001

cc:
Original NDA 21-226 and NDA 21-251
Division File
HFD-530/RPM/Belouin (with attachments)
HFD-2/MedWatch (with attachments)

(Nos. 3956 and 3959)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Memorandum of Project Manager's Review: Supplemental Labeling Review with Final Printed Labeling

NDA: 21-226/S-002
21-251/S-002

Date submitted: May 4, 2001
Date received: May 7, 2001
Date completed: May 25, 2001

Sponsor: Abbott Laboratories
D-491/AP6B-1SW
100 Abbott Park Road
Abbott Park, IL 60064-6108

Product: Kaletra™ (lopinavir/ritonavir) 133.3/33.3 mg Capsules
Kaletra™ (lopinavir/ritonavir) 80/20 mg/mL Oral Solution

Materials Reviewed:

Final Printed Label (FPL) for Supplement-002, submitted on May 4, 2001

Background

The January 2, 2001 Supplement-002 was submitted by the applicant which included modification in the oral volumes listed in the pediatric dose recommendation table contained in the **DOSAGE AND ADMINISTRATION** section of the Package Insert. The FPL dated May 4, 2001 was compared to the draft labeling approved March 13, 2001. The differences are noted below.

Revisions

1. "Tear at perforation to dispense patient information." was added under the **R_x only** heading and before the **DESCRIPTION** section heading of the Package Insert.

2. In the first sentence under the **WARNINGS** section, "**drugs**" was changed to "**medicines**" and "**not**" was capitalized to "**NOT**". The new sentence now reads, "**ALERT: Find out about medicines that should NOT be taken with KALETRA.**"

3. In the second sentence under the **Information for Patients** subsection of the **PRECAUTIONS** section of the Package Insert, "**drugs**" was changed to "**medicines**". The

sentence now reads, "**ALERT: Find out about medicines that should NOT be taken with KALETRA.**"

4. In the first sentence of the Patient Package Insert, "**drugs**" was changed to "**medicines**". The sentence now reads, "**ALERT: Find out about medicines that should NOT be taken with KALETRA.**"

Conclusions/Recommendations

The above changes to the KALETRA Final Printed Label are acceptable and are consistent with other package inserts. Final Printed Labeling is attached. An acknowledge and retain letter based on Final Printed Labeling will be issued to the applicant.

Sean J. Belouin, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

Attachment: Final Printed Labeling

Concurrence:
HFD-530/CRPM/DeCicco-TD-6/1/2001
HFD-530/MOTL/Murray-JSM-6/1/2001
HFD-530/MO/Struble-KAS-6/4/2001

cc: Original NDA 21-226 and NDA 21-251
Division File
HFD-530/RPM/Belouin (with attachments)
HFD-2/MedWatch (with attachments)

Review of Proposed Label Revision
NDAs 21,251 and 21,226 – SLR 002

Dates received: 1/3/01 and 1/31/01
Date reviewed: 3/6/01

Product: Kaletra (lopinavir/ritonavir) capsules and oral solution

Sponsor: Abbott Pharmaceutical Products Division
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-3500

Brief Review Comments:
In the 1/3/01 correspondence the sponsor proposed a slight revision in the oral volumes listed in the pediatric dose recommendation table contained in the DOSAGE AND ADMINISTRATION section of the label. These proposed changes were intended to make the oral volumes closer to the recommended mg/kg doses for children of different weight ranges.

These revisions were reviewed by the Biopharmaceutics and Clinical reviewers and felt to be appropriate. It was suggested to the sponsor that a phrase emphasizing the preference for calculating each individual's dose on a mg/kg basis be included in the dosing guidelines. This recommendation was incorporated in the 1/31/01 submission, and the final proposed label revision was acceptable to the review team. Please refer to the label review by Sean Belouin, regulatory project manager. An approval letter should be issued to the sponsor.

Linda L. Lewis, M.D.
Medical Officer
DAVDP/ODE IV/CDER/FDA

/s/

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